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EXAMINER	
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ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,352	TOOKE, NIGEL	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *9-11 and 27-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 12-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-30, in the reply filed on 9/25/2007 is acknowledged. Applicant has also elected without traverse the species of detection by means of PPi release (with claims 1-8 and 12-32 readable thereon). It is noted that the examiner inadvertently included claims 27 and 28, drawn to kits, in Group I, which is drawn to methods. Claims 27 and 28 should have been included in Group II. In addition, the examiner has rejoined Groups I and III. However, claims 29, 30, 33 and 34 are drawn to a non-elected species (detection by means of labeled nucleotides; see page 3, OA 08/09/2007). Therefore, the claim grouping is:

Group I: claims 1-26, 29, 30, 33 and 34

Group II: claims 27, 28, 31, 32 and 35

Claims 27, 28, 31, 32 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, and claims 9-11, 29, 30, 33 and 34 are withdrawn as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9/25/2007.

Applicant's remarks in the last paragraph, page 9 of the reply are noted. The examiner had concluded that AMV reverse transcriptase inherently essentially lacked RNase H activity based on Applicant's claim 12, which recites AMV RT. Upon further investigation, the examiner concedes that naturally occurring AMV RT does possess an RNase H activity, and thus claim 12 evidently refers to RNase H-deficient *derivatives* of

the recited reverse transcriptases. Nevertheless, at least claim 1 has been found obvious over the prior art. The requirement for restriction is therefore still deemed proper and made FINAL.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims recite that the primer comprises dATP (claim 19) or ATP (claim 21), wherein the dATP or ATP is exchanged for, respectively, the alpha-S analog. These claims therefore appear to recite primers comprising these analogs from the beginning (rather than as a result of the primer extension process). There is no support in the original disclosure for such subject matter. This is a NEW MATTER rejection. Applicant may overcome this rejection by pointing out support in the original disclosure that clearly indicates Applicant conceived of a primer comprising these analogs.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 12-18, 22, 23, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (US 6,210,891) in view of Melamede (US 4,863,849), Kotewicz et al (US 5,244,797) and Inouye et al (US 5,434,070).

Nyren

With regard to claims 1 and 2, Nyren teaches a method of determining the sequence of a nucleic acid molecule, comprising:

(a) providing a single stranded form of the molecule (figure 1; column 2, lines 24-45);

(b) hybridizing an oligonucleotide primer to a predetermined position of the molecule (figure 1; column 2, lines 24-45);

(c) performing at least on primer extension reaction in an extension reaction solution, whereby the oligonucleotide primer is extended on the molecule through incorporation of at least one nucleotide (figure 1; column 2, lines 24-45);

(d) detecting the presence of absence of incorporation, thereby indicating the nucleotide identity of the molecule in the relevant position (figure 1; column 2, lines 24-45);

whereby step (c) to (d) optionally are repeated (figure 1; column 2, lines 24-45).

With regard to claim 3, Nyren teaches recording (column 12, lines 65-67).

With regard to claim 4, the method of Nyren uses released pyrophosphate (PPi), which is a detectable moiety, to indicate the presence of incorporation (figure 1; column 2, lines 24-45).

With regard to claim 5, the PPi is neutralized or removed via conversion into ATP by ATP sulfurylase, which ATP is then hydrolyzed by luciferase to produce light (see figure 1).

With regard to claims 6 and 7, in Nyren's method PPi, which is a residue molecule, is released in the primer exention reaction (i.e. the incorporation of a nucleotide; see figure 1 and column 2, lines 24-45).

With regard to claim 8, Nyren teaches luciferase and ATP sulfurylase and the detection of light (see figure 1 and column 2, lines 24-45). Nyren also teaches apyrase (column 4, lines 15-26).

With regard to claim 15, Nyren teaches a pH of 7.75 (column 13, lines 3-5).

With regard to claim 17, Nyren teaches 10 mM magnesium acetate (column 13, lines 3-5). Magnesium acetate is a salt.

With regard to claim 18, Nyren teaches a DNA primer (see figure 4, "NUSPT", and column 14, lines 50-56; compare with sequence shown at column 12, line 19, "NUSPT" and SEQ ID NO:3 of the sequence listing, identifying the sequence as DNA).

With regard to claim 23, Nyren teaches it is desirable to amplify the nucleic acid being sequenced (column 4, lines 39-42).

With regard to claim 25, Nyren teaches capturing the nucleic acid to be sequenced is captured to a solid phase by an immobilized oligonucleotide (column 8, lines 13-16).

With regard to claim 26, Nyren teaches that in his method, "the luminescence output was calibrated by the addition of a known amount of ATP or PPi" (column 13, lines 1-3). Therefore, Nyren's results obtained during nucleotide incorporation are inherently compared to a reference (the reference being the known amount of ATP or PPi with which the instrument was calibrated).

Nyren does not teach that the nucleic acid being sequenced is RNA, that the method is performed in the presence of an RNase-inhibiting agent, or that the polymerase is a reverse transcriptase essentially lacking RNase H activity, as recited in claim 1.

With regard to claim 12, Nyren does not teach a reverse transcriptase from among those recited.

With regard to claim 13, Nyren does not teach a mixture of RNA dependent polymerases.

With regard to claim 14, Nyren does not teach performing the extension at a temperature within the recited range.

With regard to claim 16, Nyren does not a nucleotide concentration within the recited range.

With regard to claim 22, Nyren does not teach any of the recited compounds being present during the primer extension reaction.

Melamede

With regard to claim 1, Melamede also teaches sequencing a nucleic acid by annealing a primer to a template, performing a primer extension reaction, and detecting incorporation (see figure 2, for example). Melamede also teaches at column 8, lines 25-36 (emphasis provided):

"The single-stranded DNA or RNA molecule to be sequenced is primed at a specific site with a short oligonucleotide primer. The primed template and a template-directed polymerase are placed in a reaction chamber that allows for separation of unreacted nucleotide precursors from the primed template and the polymerase. If the template is a single-stranded DNA molecule, a DNA-directed DNA or RNA polymerase may be used; if the template is a single-stranded RNA molecule, then a reverse transcriptase (i.e., an RNA directed DNA polymerase) may be used."

With regard to claim 12, Melamede teaches AMV RT (column 11, lines 60-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify Nyren's method to sequence RNA molecules by substituting an RNA molecule for the DNA molecule template used by Nyren, and to substitute a reverse transcriptase, such as AMV RT, for the polymerase used by Nyren. This would have been obvious because Melamede teaches sequencing RNA molecules using AMV RT, and the only difference between the methods of Nyren and Melamede is how the incorporation was detected. Since

pyrophosphate is released upon incorporation of ribonucleotides (just as is the case for deoxyribonucleotides), one would have had a reasonable expectation of success in substituting RNA templates and reverse transcriptase into the method of Nyren, to gain the added benefit of sequencing RNA.

With regard to claim 13, it would also have been obvious to use mixtures of RNA dependent polymerases, since this would simply represent combining equivalents (i.e. different reverse transcriptases) known for the same purpose (see MPEP 2144.06).

With regard to claim 23, it would also have been obvious to amplify the RNA prior to sequencing, since Nyren taught it was desirable to amplify the nucleic acid to be sequenced in situations where the amount of sample available was small (column 4, lines 39-42). One of skill in the art would have recognized amplification would also have been of benefit when the sample to be sequenced was RNA.

Kotewicz

With regard to claim 1, Kotewicz teaches a reverse transcriptase that essentially lacks RNase H activity (column 2, lines 49-51).

With regard to claim 12, Kotewicz enzyme was derived from M-MuLV (i.e. M-MLV; column 11, lines 9-15).

With regard to claim 14, Kotewicz uses this enzyme to perform primer extension from an RNA template at 37°C (column 14, lines 17-18).

With regard to claim 15, Kotewicz uses this enzyme to perform primer extension from an RNA template at pH 8.3 (column 14, line 13).

With regard to claim 16, Kotewicz uses this enzyme to perform primer extension from an RNA template at a nucleotide concentration of 0.5 mM (column 14, lines 14-15).

With regard to claim 17, Kotewicz uses this enzyme to perform primer extension from an RNA template at salt (KCl) concentration of 75 mM (column 14, line 13).

With regard to claim 18, Kotewicz uses this enzyme to perform primer extension from an RNA template using a DNA primer $(dT)_{12-18}$ (column 14, lines 17-18).

With regard to claim 22, Kotewicz uses this enzyme to perform primer extension from an RNA template in the presence of actinomycin D (column 14, line 35).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the RNase deficient reverse transcriptase taught by Kotewicz for the purpose of sequencing an RNA molecule by the method suggested by the combined teachings of Nyren and Melamede. One would have been motivated to do so, because Kotewicz teaches that RNase H activity is a major problem when using reverse transcriptase to synthesize cDNA (column 1, line 47 through column 2, line 5). Since cDNA synthesis is precisely what would be occurring in the embodiment of sequencing taught by Melamede: "if the template is a single-stranded RNA molecule, then a reverse transcriptase (i.e., an RNA directed DNA polymerase) may be used" (column 8, lines 25-36), the problem solved by Kotewicz would clearly have applied to the case of sequencing as suggested by the combined teachings of Nyren and Melamede.

It would also have been obvious to use the conditions of temperature, pH, salt and nucleotide concentrations, and actinomycin D concentration (claims 14-17 and 22)

taught by Kotewicz when using this enzyme, since Kotewicz already showed these were appropriate conditions.

Inouye

With regard to claim 1, Inouye teaches at column 12, line 66 through column 13, line 9 (emphasis provided):

"For background and protocols on synthesis of cDNA and reverse transcript, see Molecular Cloning: A Laboratory Manual ("Maniatis") pages 129-130 and 213-216 (incorporated herein by reference). If it is desired to separate any RNase activity when such is present, the protocols referred to in Maniatis in the Chapter on Synthesis of cDNA may be referred to (page 213). See also Marcus et al., J. Virol., 14, 853 (1974) and other references cited at page 213. Other protocols are known in the art, such as including in the reverse transcription reaction mixture an inhibitor of RNase, such as vanadyl-ribonucleoside complexes or RNasin."

Furthermore, the art is replete with examples of the inclusion of RNase inhibitors in reverse transcription reactions.

It would have been *prima facie* obvious to one of ordinary skill in the art to use an RNase inibitor when practicing the RNA sequencing method suggested by the combined teachings of Nyren, Melamede and Kotewicz, since it was known in the art that RNA was susceptible to RNase degradation, and Inouye teaches it was known in the art, in the context of a reverse transcriptase reaction, to add inhibitors of RNase.

Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (US 6,210,891) in view of Melamede (US 4,863,849), Kotewicz et al (US 5,244,797) and Inouye et al (US 5,434,070) as applied to claims 1-8, 12-18, 22, 23, 25 and 26 above, and further in view of Myers et al (PNAS 77(3):1316-1320, March 1980).

The teachings of Nyren, Melamede, Kotewicz and Inouye have been discussed. These references do not teach using an RNA primer.

Myers teaches that reverse transcriptases can use RNA as a primer (see title, for example).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use either DNA or RNA as the primer when practicing the method for sequencing RNA suggested by the combined teachings of Nyren, Melamede, Kotewicz and Inouye, since these are the only two options and both were known in the prior art to be suitable for primer extension by reverse transcriptase. See MPEP 2144.07 regarding the selection of a known material based on its suitability for its intended purpose.

Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (US 6,210,891) in view of Melamede (US 4,863,849), Kotewicz et al (US 5,244,797) and Inouye et al (US 5,434,070) as applied to claims 1-8, 12-18, 22, 23, 25 and 26 above, and further in view of Malek et al (US 5,665,545).

The teachings of Nyren, Melamede, Kotewicz and Inouye have been discussed. These references do not teach using rITP in place of rGTP during amplification of the RNA.

Malek teaches a method of amplifying RNA called TRAM (terminal repeat amplification method) and teaches that substitution of rITP for rGTP in an RNA amplification product alleviates pausing of reverse transcriptase due to secondary structure (stem-loop formation) when using the RNA in a subsequent primer extension reaction (column 24, lines 21-45).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to use the known method of RNA amplification taught by Malek when practicing the method for sequencing RNA suggested by the combined teachings of Nyren, Melamede, Kotewicz and Inouye, since Nyren teaches the desirability of amplifying the nucleic acid to be sequenced (column 4, lines 39-42). Furthermore, it would have been obvious to exchange rITP for rGTP to produce an RNA amplification product, as Malek shows that such a product reduces pausing of the reverse transcriptase during primer extension.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

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